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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/814,025	03/31/2004	James Rasmussen	GC22.4-CON2	4968

24536 7590 01/19/2006
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EXAMINER

SULLIVAN, DANIEL M

ART UNIT PAPER NUMBER

1636

DATE MAILED: 01/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

This Office Action is a reply to the Paper filed 10 November 2005 in response to the Non-Final Office Action mailed 8 July 2005. Claims 48-59 and 63-72 were withdrawn from consideration and claims 60-62 were considered in the 8 July Office Action. Claims 48-72 are pending and claims 60-62 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment and Arguments

Priority

Amendment of the specification to remove 07/289,589 application from the priority claim is acknowledged. However, the application contains an application data sheet, which identifies the '589 application as a parent of the instant case. As an application data sheet, when present, is the controlling document with regard to priority, the amendment to the specification does not remove the '589 application from the priority chain. In order to remove the '589 application, Applicant must file a substitute application data sheet which does not claim benefit of the '589 application.

Claim Rejections - 35 USC § 112

Claims 60-62 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

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described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record and herein below in the response to arguments.

Response to Arguments

The previous Office Action concludes finds, based on a review of the record as a whole, that in view of the tremendous scope of the claims, the unpredictable nature of glycosylation in mammalian cells and the failure of the specification to provide a detailed description of the claimed invention beyond the scope of a CHO cell transformed with a plasmid selected from the group consisting of PGB20, PGB37 and PGB42, the skilled artisan would conclude that Applicant was not in possession of the full scope of the claimed invention at the time the application was filed.

In response to the *prima facie* case of record, Applicant has amended the claims such that the glucocerebrosidase enzyme is limited to a human glucocerebrosidase and asserts that the claims only cover the glucocerebrosidase enzyme found in humans. However, as pointed out in the previous Office Action (page 6), specification teaches that the glucocerebrosidase of the claims encompasses all enzymes having an enzyme activity which causes hydrolysis of a glucocerebroside. Thus, the claims encompass any enzyme having glucocerebrosidase activity regardless of the structure thereof. The limitation of the enzyme to being "human" merely suggests that the enzyme is native to humans. However, beyond the scope of a plasmid selected from the group consisting of PGB20, PGB37 and PGB42 and the human placental glucocerebrosidase (which is the species actually discussed in the section at page 1, line 23 to

page 2 line 6 cited by applicant in support of the limitation) the specification does not disclose a representative number of species or the relevant identifying characteristics that define a genus of any human enzyme having an activity which causes hydrolysis of a glucocerebroside.

The previous Office Action additionally found that the specification has not described the therapeutically useful embodiments claimed. As stated in the Office Action, the specification teaches, prophetically, that rGCR having an appropriate carbohydrate structure can be produced by introducing GCR-encoding DNA into any vertebrate or invertebrate cell and treating the cell with inhibitors of carbohydrate processing (bridging pages 27-28). However, the specification also teaches that, to be therapeutically useful as recited in the claims, the glucocerebrosidase must be post-translationally modified to provide a carbohydrate structure which will target to human mannose receptors (see especially the paragraph bridging page 26-27). The specification further teaches that such a glucocerebrosidase has at least two carbohydrate moieties each having a Man₃-Man₉ structure and such rGCR represents at least 50% of the rGCR provided in the therapeutic composition (page 27, lines 1-4). However, the specification provides no specific disclosure of which combination within the broad scope of a glucocerebrosidase produced by any mammalian cell exposed to any inhibitor of carbohydrate processing that acts to inhibit conversion of Glc₃Man₉GlcNac₂ to smaller species will comprise the requisite carbohydrate structure.

The Office Action cites Houdebine *et al.* (2000) *Transgen. Res.* 9:305-320 as teaching that the glycosylation pattern of a polypeptide in any given mammalian cell are complex and unpredictable, particularly when the polypeptides are produced in the amounts sufficient for pharmaceutical use.

In response, Applicant points out that the claims are directed to production of the glucocerebrosidase *in vitro* and contends that, in contrast to transgenic production *in vivo*, the skilled artisan is able to control glycosylation processes in the cell *in vitro*. Applicant urges that treatment of cultured cells with inhibitors of carbohydrate processing that act to inhibit the conversion of $\text{Glc}_3\text{Man}_9\text{GlcNac}_2$ to smaller species leads to production of glucocerebrosidase with exposed mannose residues having higher affinity for the human mannose receptor. However, no evidence is provided to support these assertions and, as pointed out in the previous Office Action, the application does not contain a working example of a single enzyme produced by the method recited in the claim. Beyond the scope of a CHO cell comprising an enzymatically active human glucocerebrosidase, said cell being transformed with a plasmid selected from the group consisting of PGB20, PGB37 and PGB42, the application fails to disclose the properties of any enzyme produced by the method recited in the claims such that the skilled artisan would recognize that applicant was in possession of any glucocerebrosidase enzyme produced by any cell from any of the more than 5,000 species of mammal, wherein the cell is exposed to any inhibitor of carbohydrate processing that acts to inhibit conversion of $\text{Glc}_3\text{Man}_9\text{GlcNac}_2$ and wherein the glucocerebrosidase has the properties identified as critical to use in the treatment of Gaucher's disease in a human patient.

Finally, Applicant contends that the specification teaches methods for analyzing the sugar structures on glucocerebrosidase and teaches methods to determine the ability of glucocerebrosidase to bind and be taken up by macrophages. However, as stated in the previous Office Action (page 9), it is not sufficient to define an enzyme solely by its principal biological property (*i.e.* it has an enzyme activity which causes hydrolysis of a glucocerebroside and is

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useful in the treatment of Gaucher's disease in humans) because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any glucocerebrosidase with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all glucocerebrosidases that achieve a result without defining what means will do is not in compliance with the description requirement.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §112, first paragraph, as lacking written description.

Rejection of claims 60-62 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in part and maintained in part. Specifically, the claims are rejected because the specification, while being enabling for a pharmaceutical composition suitable for the treatment of a human patient having Gaucher's disease comprising a human placental glucocerebrosidase produced by providing a culture of CHO cells capable of expressing said human placental glucocerebrosidase and treating the CHO cells with deoxymannojirimycin, swainsonine, castanospermine, deoxy-nojirimycin or N-methyl-deoxynojirimycin, does not reasonably provide enablement for the broad scope of a pharmaceutical composition suitable for the treatment of a human patient having Gaucher's disease comprising a human placental glucocerebrosidase produced by providing a culture of any mammalian cell capable of expressing any human glucocerebrosidase and treating the cell with any inhibitor or carbohydrate processing that acts to inhibit conversion of $\text{Glc}_3\text{Man}_9\text{GlcNac}_2$

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to smaller species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The reasoning for this rejection is the same as the reasoning set forth in the previous Office Action. In brief, the Office Action determined based on an analysis of the factual inquiries set forth in *In re Wands* that, although the relative level of skill in the art is high, the skilled artisan would not be able to make and use the claimed invention based on the instant disclosure and the teachings available in the art. The claims are tremendously broad, encompassing any polypeptide capable of hydrolyzing a glucocerebroside isolated from any mammalian cell wherein conversion of $\text{Glc}_3\text{Man}_9\text{GlcNac}_2$ to smaller species has been inhibited. However, given the absence of an adequate disclosure of the features that define a genus of any polypeptide capable of hydrolyzing a glucocerebroside and the unpredictability of glycosylation in mammalian cells, the skilled artisan would have to make and test each species within an essentially unlimited genus of polypeptides for the function recited in the claims. Given the high degree of unpredictability that is a general feature of developing any effective therapy, the amount of experimentation required to develop the invention such that it could be made and used as recited in the claims would be undue.

Response to Arguments

In response to the *prima facie* rejection of record, Applicant has amended the claim to recite that the claimed glucocerebrosidase is a “human” glucocerebrosidase and in the remarks (bridging pages 9-10) cites the arguments set forth in response to the written description

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requirement as addressing the Examiner's comments as to the unpredictable nature of the invention.

As discussed above, Applicant's argument that production of the glucocerebrosidase *in vitro*, in contrast to transgenic production *in vivo*, allows one to control glycosylation processes in the cell. Applicant urges that treatment of cultured cells with inhibitors of carbohydrate processing that act to inhibit the conversion of $\text{Glc}_3\text{Man}_9\text{GlcNac}_2$ to smaller species leads to production of glucocerebrosidase with exposed mannose residues having higher affinity for the human mannose receptor. However, no evidence is provided to support these assertions and, as pointed out in the previous Office Action, the application does not contain a working example of a single enzyme produced by the method recited in the claim. As described in the previous Office Action, Houdebine teaches that the reasons why some proteins are not correctly glycosylated in heterologous expression systems are particularly complex and might be related to the superphysiological production of the recombinant proteins. There is nothing of record that to suggest that glycosylation of superphysiologically expressed proteins is more predictable *in vitro* than in the cellular systems described by Houdebine. The amended claims are still tremendously broad and given the unpredictable nature of the art, which is supported by the evidence presently of record, the skilled artisan would have to make and test a tremendous number of species in order to identify the pharmaceutically useful embodiments within the scope of the claim. Therefore, the amount of experimentation required to make the full scope of what is claimed is undue.

With regard to pharmaceutical application, Applicant's arguments are persuasive to the extent that claims limited to a pharmaceutical composition suitable for the treatment of a human

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patient having Gaucher's disease comprising a human placental glucocerebrosidase produced by providing a culture of CHO cells capable of expressing said human placental glucocerebrosidase and treating the CHO cells with deoxy-mannojirimycin, swainsonine, castanospermine, deoxy-nojirimycin or N-methyl-deoxynojirimycin.

Applicant's arguments have been fully considered but are not deemed persuasive, in view of the record as a whole, with regard to establishing that the disclosure is enabling for the full scope of what is presently claimed. Therefore, the claims stand rejected under 35 USC §112, first paragraph, as lacking enablement.

Double Patenting

Rejection of claims 60-62 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,451,600 is withdrawn in view of the filing of a terminal disclaimer.

Claim Rejections - 35 USC § 102

Rejection of claims 60-62 under 35 U.S.C. 102(b) as being anticipated by Aerts *et al.* (1986) *Biochem. Biophys. Res. Commun.* 141:452-458 is withdrawn in view of the limitation of the claims to being suitable for the treatment of a human patient having Gaucher's disease and Applicant's arguments.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Daniel M. Sullivan, Ph.D.
Examiner
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DAVID GUZO
PRIMARY EXAMINER